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四个对映-贝壳杉烷型二萜化合物结构，NMR和红外光谱实验和量子化学的研究

Experimental and quantum chemical studies on the structure, NMR and vibrational spectra of four ent-kaurene diterpenoids

汪涛

指导教师：陈忠

专业名称：物理化学(含化学物理)

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摘 要

香茶菜属(Isodon)植物属于唇形科(Labiatae)，主要分布于亚洲和非洲，该属在我国有90多种.分怖于全国各地，是中国民间广泛采用的草药。该类植物含有对映-贝壳杉型二萜化合物，研究表明这类化合物具有良好的生物活性如消炎，抗菌和抗癌等活性。

本工作从三种香茶菜属植物中提取分离筛选出具有生物活性的化合物，特别是具有对映-贝壳杉烷二萜化合物的结构， 结合实验和量子化学计算方法研究其分子结构，NMR化学位移，红外光谱(IR)以及其它如表面分子静电位(MEP)和前线分子轨道(HOMO，LJMO)等物理化学性质，为深入研究细胞毒活性的作用机理提供必要的基础数据。

本文主要工作包括:

1. 从三种具有抗癌活性的香茶菜植物总序香茶菜，毛叶香茶菜和维西香茶菜中提取分离出具有代表性的对映-贝壳杉烯型二萜化合物，采用硅胶柱层析纯化等分离手段，并使用各种近代物理方法(IR， ，1H，13NMR，MS)鉴定分离出化合物的结构。在此基础上结合量子化学方法对其中四个对映-贝壳杉型化合物进行量子化学计算。这四个化合物是Weisiensin B， Epinodosinol和Epinodosin (7-断裂-对映-贝壳杉烯型延命素型) 及Kamebacetal A。

测试了Weisiensin B化合物对人体肿瘤的细胞毒作用，并通过慧星电泳实验评估了受试化合物对Bel-7402细胞的DNA损伤能力。

2. 选用所研究的化合物的晶体衍射数据作为初始构型，用HF及B3LYP密度泛函方法和有无溶剂存在下，在不同基组水平上，对其几何构型进行全优化，将优化好的结构参数的计算值与从X-光衍射得出实验值(键长，键角和二面角)进行比较，结果表明不论HF或DFT方法其计算值都与实验值的符合程度相当好；计算结果还表明溶剂介质对几何参数的影响相当小。

3. 在几何优化的构型基础上，采用规范不变原子轨道GIAO方法，分别采用HF和DFT方法，不同的基组以及在气相中和溶剂存在下(IEFPCM)计算各分子的NMR的化学位移。并将计算值与实验值进行比较，通过线性回归，进行统计误差分析。结果表

明DFT方法由于充分考虑电子相关，其相关系数R一般高于HF方法，表明DFT对于这类化合物的化学位移的计算比HF方法更好。归属了红外振动光谱各振动谱带，为了使计算出的IR频率值与实验值符合更好，在计算中引入校正系数。被测分子几何结构，NMR参数和红外光谱的符合程度说明计算方法的可靠性。

4. 在优化好的几何构型基础上，用HF及B3LYP密度泛函方法，用不同基组，对所研究的化合物的分子静电势进行理论计算，通过计算在真空和有溶剂存在条件下的质子化能以阐明介质对质子化能大小的的影响。根据表面静电位推测出该类化合物可能的活性中心。

5. 研究结果表明DFT和HF方法可用来研究结构复杂的对映-贝壳杉型化合物的几何结构，NMR化学位移和红外振动光谱的归属。

关键词：香茶菜属；对映-贝壳杉烷型二萜；密度泛函理论；分子静电位；振动光谱

Abstract

Isodon is a kind of herbal medicines which is widely used in Chinese folk. It belongs to the family of Labiatae, there are more than 90 species distributed throughout our country. Such plants contain ent-kaurane diterpenoid compunds. A large number of studies have shown that this class of compounds exhibit good biological activity such as the anti-inflammatory and antimicrobial activiy. It was used as the common folk anticancer agents.

Compounds with biological activity, especially compounds with ent-kaurane diterpenoid structure, were selected from plants of Isodon by means of separation and extraction. The molecular structure, NMR chemical shifts, IR and other physicochemical properties such as the molecular electrostatic potential(MEP),HOMO and LUMO were studied by experimental and theoretical calculations, which can supply necessary fundamental data for the in-depth study of the mechanisms of the cytotoxic activitives.

In this work, ent-kaurane diterpenoid compounds were extracted and separated by chromatographic technique from three different kinds of Isodon plants possessing anticancer activity, They are Isodon racemosa (Hemsl) Hara ,Isodon japonica (Burm.f) Hara var. galaucocalyx (maxin) Hara and Isodon weisiensis C.Y. Wu. The structure of the compounds isolated was identified by a variety of modern physical mehods (IR, 1H, 13NMR, MS) by using silica column chromatography and other separation methods. Their partial biological activity was tested as well. On this basis, combined with theoretical methods, four ent-kaurane diterpenoid compounds were studied by quantum chemical calculation. The isolated diterpenoids can rarely form a single crystal, thus, the following four compounds which can form single crystals were selected in this study. They are Weisiensin B, Epinodosinol, Epinodosin and KamebacetalA.

Tested Weisiensin B on human tumor cytotoxicity and evaluated DNA damage

potential of Weisiensin B by comet assay.

The theoretical part including:

1. Initial configurations were taken from crystal diffraction data of the studied compounds and their geometries have been fully optimized by HF and density functional B3LYP methods in with or without solvent environment using different basis sets. The optimized structural parameters (bond lengths, bond angles, dihedral angles) have been compared with the experimental ones from X-ray diffraction. Results show that the experimental and calculated values are in good agreement in both HF and DFT methods.

2. On the basis of the geometry optimization, the gauge-including atomic orbital (GIAO) method was adopted by HF and DFT calculations using different basis sets in gas phase and in solvent environment to determine NMR chemical shifts of the studied compounds. The theoretical results were compared with experimental data by linear regression and the statistical error was analysed finally. Results indicate that the correlatin coefficient R calculated by DFT is generally higher than the HF mehod, probably due to the fact that the former adequately takes into account of the contributions of electron correlation, that is to say, DFT is superior to HF mehod in the calculation of this class of compounds. The vibrational bands of IR spectra were well assigned, in order to make IR frequencies calculated fit better with the experimental one, scaled factors were introduced in the calculation. The geometric structure of the studied molecules, the NMR parameters and IR spectra correspond well with experimental data, this indicates that the calculation method employing by us is reliable.

3. On the basis of the well optimized geometry, molecular electrostatic potential of the studied compounds was calculated by density functional B3LYP and HF methods employing different basis sets. The effects of medium on protonated energy can be implicated by different values calculated in vacuum and in solvent environment. The probable active center can be predicted according to the

surface electrostatic potential.

4. The results show DFT and HF methods applicable to study the geometrical structure,assignments of NMR chemical shifts and the vibrational spectrum for the complex ent-kaurane compounds.

Keywords: Isodon; ent-kaurane diterpenoid; density functional theory; molecular electrostatic potential; vibrational spectrum

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